

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a therapeutically effective amount of a tissue protective cytokine; at least one anti-inflammatory agent; and a pharmaceutically acceptable carrier.
2. The pharmaceutical composition of claim 1, wherein the anti-inflammatory agent is selected from the group consisting of corticosteroids, glucocorticoids, steroids, non-steroidal anti-inflammatory drugs, beta-agonists, anticholinergic agents, methyl xanthines, gold injections, sulphasalazine, penicillamine, anti-angiogenic agents, dapsone, psoralens, anti-malarial agents, anti-viral agents, and antibiotics.
3. A pharmaceutical composition comprising a therapeutically effective amount of a tissue protective cytokine; at least one immunomodulatory agent; and a pharmaceutically acceptable carrier.
4. The pharmaceutical composition of claim 3, wherein the anti-inflammatory agent is selected from the group consisting of methotrexate, leflunomide, cyclophosphamide, cytoxan, Immuran, cyclosporine A, minocycline, azathioprine, antibiotics, methylprednisolone, corticosteroids, steriods, mycophenolate mofetil, rapamycin, mizoribine, deoxyspergualin, brequinar, malononitriloamindes, T cell receptor modulators, and cytokine receptor modulators.
5. A pharmaceutical composition of claim 1 or 3, wherein said tissue protective cytokine is selected from the group consisting of i) an erythropoietin that lacks sialic acid moieties; ii) an erythropoietin that lacks N-linked or lacks O-linked carbohydrates; iii) an erythropoietin having a reduced carbohydrate content by treatment of native erythropoietin with at least one glycosidase; iv) an erythropoietin having at least one or more oxidized carbohydrates; v) an erythropoietin comprising at least one or more oxidized carbohydrates which is chemically reduced; vi) an erythropoietin comprising at least one or more modified arginine residues; vii) an erythropoietin comprising at least one or more modified lysine residues or a modification of

the N-terminal amino group of the erythropoietin molecule; viii) an erythropoietin comprising at least a modified tyrosine residue; ix) an erythropoietin comprising at least a modified aspartic acid or a glutamic acid residue; x) an erythropoietin comprising at least a modified tryptophan residue; xi) an erythropoietin having at least one amino group removed; xii) an erythropoietin comprising at least an opening of at least one of the cystine linkages in the erythropoietin molecule; and xiii) a truncated erythropoietin.

6. A method for treating inflammation in a mammal comprising responsive cells, tissues, and/or organs, said method comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of a tissue protective cytokine and a pharmaceutically acceptable carrier.

7. The method of Claim 6, wherein the tissue protective cytokine lacks at least one activity selected from the group consisting of increasing hematocrit, vasoconstriction, hyperactivating platelets, pro-coagulant activity and increasing production of thrombocytes.

8. A method treating inflammation in a mammal comprising responsive cells, tissues, and/or organs, said method comprising administering to a mammal in need thereof a pharmaceutical composition comprising a prophylactically or therapeutically effective amount of a tissue protective cytokine and a pharmaceutically acceptable carrier, and administering to the mammal a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents or immunomodulatory agents.

9. The method of claim 8, wherein the anti-inflammatory agent is selected from the group consisting of a corticosteroid, a glucocorticoid, a steroid, a non-steroidal anti-inflammatory drug, a beta-agonist, a anticholinergic agent, a methyl xanthine, gold injection, a sulphasalazine, penicillamine, a anti-angiogenic agent, dapsone, psoralen, a anti-malarial agent, a anti-viral agent, and an antibiotic.

10. The method of claim 8, wherein the immunomodulatory agent is selected from the group consisting of a proteinaceous agent, a peptide mimetic, an antibody, a nucleic acid molecule, a small molecule, an organic compound, an inorganic compound, methotrexate, leflunomide, cyclophosphamide, cytoxin, Immuran, cyclosporine A, minocycline, azathioprine, an antibiotic, methylprednisolone (MP), a corticosteroid, a steroid, mycophenolate mofetil, rapamycin, mizoribine, deoxyspergualin, brequinar, a malononitroloamide, a T cell receptor modulator, and a cytokine receptor modulator.

11. The method of claim 6 or 8, wherein said tissue protective cytokine is i) an erythropoietin that lacks sialic acid moieties; ii) an erythropoietin that lacks N-linked or lacks O-linked carbohydrates; iii) an erythropoietin having a reduced carbohydrate content by treatment of native erythropoietin with at least one glycosidase; iv) an erythropoietin having at least one or more oxidized carbohydrates; v) an erythropoietin comprising at least one or more oxidized carbohydrates which is chemically reduced; vi) an erythropoietin comprising at least one or more modified arginine residues; vii) an erythropoietin comprising at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule; viii) an erythropoietin comprising at least a modified tyrosine residue; ix) an erythropoietin comprising at least a modified aspartic acid or a glutamic acid residue; x) an erythropoietin comprising at least a modified tryptophan residue; xi) an erythropoietin having at least one amino group removed; xii) an erythropoietin comprising at least an opening of at least one of the cystine linkages in the erythropoietin molecule; and xiii) a truncated erythropoietin.

12. The method of claim 6 or 8, or wherein said tissue protective cytokine is asialoerythropoietin or phenylglyoxal-erythropoietin.

13. The method of claim 6 or 8, wherein the tissue protective cytokine is capable of traversing an endothelial cell barrier.

14. The method of claim 13, wherein the endothelial cell barrier is selected from the group consisting of blood-brain barrier, blood-eye barrier, blood-testis barrier, blood-ovary barrier, and blood-uterus barrier.

15. The method of claim 6 or 8, wherein responsive cells, tissues, and/or organs in the mammal, are selected from the group consisting of neuronal cells, muscle cells, heart, lung, liver, kidney, small intestine, adrenal cortex, adrenal medulla, capillary cells, endothelial cells, testes, ovary, endometrial cells, and stem cells.

16. The method of claim 6 or 8, wherein the responsive mammalian cells further comprise cells selected from the group consisting of photoreceptor cells, ganglion cells, bipolar cells, horizontal cells, amacrine cells, Müller cells, myocardium cells, pace maker cells, sinoatrial node cells, sinoatrial node cells, sinus node cells, atrioventricular node cells, bundle of His cells, hepatocyte cells, stellate cells, Kupffer cells, mesangial cells, goblet cells, intestinal gland cells, enteral endocrine cells, glomerulosa cells, fasciculate cells reticularis cells, chromaffin cells, pericyte cells, Leydig cells, Sertoli cells, sperm cells, Graffian follicle cells, primordial follicle cells, endometrial stroma cells, and endometrial cells.

17. The method of claim 6 or 8, wherein said tissue protective cytokine is asialoerythropoietin.

18. The method of claim 17, wherein said asialoerythropoietin is human asialoerythropoietin.

19. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin with no N-linked carbohydrates.

20. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin with no O-linked carbohydrates.

21. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin treated with at least one glycosidase.
22. The method of claim 6 or 8, wherein said tissue protective cytokine is periodate-oxidized erythropoietin.
23. The method of claim 22, wherein said periodate-oxidized erythropoietin is chemically reduced with sodium cyanoborohydride.
24. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin comprising a R-glyoxal moiety on the one or more arginine residues, wherein R is aryl or alkyl moiety.
25. The method of claim 24, wherein said erythropoietin is phenylglyoxal-erythropoietin.
26. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin in which at least one arginine residue is modified by reaction with a vicinal diketone selected from the group consisting of 2,3-butanedione and cyclohexanedione.
27. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin in which at least one arginine residue is reacted with 3-deoxyglucosone.
28. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin molecule comprising at least one biotinylated lysine or N-terminal amino group.
29. The method of claim 28, wherein said erythropoietin molecule is biotinylated erythropoietin.
30. The method of claim 6 or 8, wherein said tissue protective cytokine is a glucitoyl lysine erythropoietin or a fructosyl lysine erythropoietin.

31. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin having at least one carbamylated lysine residue.

32. The method of claim 31, wherein said carbamylated erythropoietin is selected from the group consisting of alpha-N-carbamoylerythropoietin; N-epsilon-carbamoylerythropoietin; alpha-N-carbamoyl, N-epsilon-carbamoylerythropoietin; alpha-N-carbamoylasialoerythropoietin; N-epsilon-carbamoylasialoerythropoietin; alpha-N-carbamoyl, N-epsilon-carbamoylasialoerythropoietin; alpha-N-carbamoylhyposialoerythropoietin; N-epsilon-carbamoylhyposialoerythropoietin; and alpha-N-carbamoyl, N-epsilon-carbamoylhyposialoerythropoietin.

33. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin in which at least one lysine residue is acylated.

34. The method of claim 33, wherein a lysine residue of said erythropoietin is acetylated.

35. The method of claim 34, wherein said acetylated erythropoietin is selected from the group consisting of alpha-N-acetylerythropoietin; N-epsilon-acetylerythropoietin; alpha-N-acetyl, N-epsilon-acetylerythropoietin; alpha-N-acetylasialoerythropoietin; N-epsilon-acetylasialoerythropoietin; alpha-N-acetylhyposialoerythropoietin; N-epsilon-acetylhyposialoerythropoietin; and alpha-N-acetyl, N-epsilon-acetylhyposialoerythropoietin.

36. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin comprising a succinylated lysine residue.

37. The method of claim 36, where said erythropoietin is selected from the group consisting of alpha-N-succinylerythropoietin; N-epsilon-succinylerythropoietin; alpha-N-succinyl, N-epsilon-succinylerythropoietin; alpha-N-succinylasialoerythropoietin; N-epsilon-succinylasialoerythropoietin; alpha-N-succinyl, N-epsilon-succinylasialoerythropoietin; alpha-N-succinyl, N-epsilon-succinylasialoerythropoietin; alpha-

N-succinylhyposialoerythropoietin; N-epsilon-succinylhyposialoerythropoietin; and alpha-N-succinyl, N-epsilon-succinylhyposialoerythropoietin.

38. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin with at least one lysine residue modified by a 2, 4, 6-trinitrobenzenesulfonic acid salt.

39. The methods of claim 38, wherein the salt is 2, 4, 6-trinitrobenzenesulfonate sodium.

40. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin in which at least one tyrosine residue is nitrated and/or iodinated.

41. The method of claim 6 or 8, wherein said tissue protective cytokine is an erythropoietin in which an aspartic acid and/or glutamic acid residue is reacted with a carbodiimide followed by reaction with an amine.

42. The method of claim 41, wherein said amine is glyciamide.

43. The method of claim 6 or 8, wherein the inflammation results from a disease condition or trauma.

44. The method of claim 43, wherein the trauma is selected from the group consisting of angitis, chronic bronchitis, pancreatitis, osteomyritis, rheumatoid arthritis, glomerulonephritis, optic neuritis, temporal arteritis, encephalitis, meningitis, transverse myelitis, dermatomyositis, polymyositis, necrotizing fascilitis, hepatitis, and necrotizing enterocolitis.

45. The method of claim 6 or 8, wherein the tissue protective cytokine inhibits inflammation resulting from cytokines produced by glial cells.

46. The method of claim 6 or 8, wherein the inflammation is triggered by apoptosis.

47. Use of a tissue protective cytokine for the preparation of a pharmaceutical composition for treating inflammation in a mammal comprising responsive cells, tissues, and/or organs.

48. The use of Claim 47, wherein the tissue protective cytokine lacks at least one activity selected from the group consisting of increasing hematocrit, vasoconstriction, hyperactivating platelets, pro-coagulant activity, and increasing production of thrombocytes.

49. The use of claim 47, wherein the inflammation results from a disease condition or trauma.

50. The use of claim 49, wherein the trauma is caused by a seizure disorder, multiple sclerosis, stroke, hypotension, cardiac arrest, ischemia, myocardial infarction, age-related loss of cognitive function, radiation damage, cerebral palsy, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Leigh disease, AIDS dementia, memory loss, amyotrophic lateral sclerosis, alcoholism, mood disorder, anxiety disorder, attention deficit disorder, autism, Creutzfeld-Jakob disease, brain trauma, spinal cord trauma, brain ischemia, spinal cord ischemia, heart-lung bypass, chronic heart failure, macular degeneration, diabetic neuropathy, diabetic retinopathy, glaucoma, retinal ischemia, or retinal trauma.

51. Use of a tissue protective cytokine for the preparation of a pharmaceutical composition for treating inflammation in a mammal comprising responsive cells, tissues, and/or organs, wherein the pharmaceutical composition comprises a therapeutically effective amount of a tissue protective cytokine; at least one anti-inflammatory agent or immunomodulatory agent; and a pharmaceutically acceptable carrier.

52. The use of claim 47, wherein said tissue protective cytokine is i) an erythropoietin that lacks sialic acid moieties; ii) an erythropoietin that lacks N-linked or lacks O-linked carbohydrates; iii) an erythropoietin having a reduced carbohydrate content by treatment of native erythropoietin with at least one glycosidase; iv) an erythropoietin having at least one or more oxidized carbohydrates; v) an erythropoietin comprising at least one or more oxidized carbohydrates which is chemically reduced; vi) an erythropoietin comprising at least one or more modified arginine residues; vii) an erythropoietin comprising at least one or more modified

lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule; viii) an erythropoietin comprising at least a modified tyrosine residue; ix) an erythropoietin comprising at least a modified aspartic acid or a glutamic acid residue; x) an erythropoietin comprising at least a modified tryptophan residue; xi) an erythropoietin having at least one amino group removed; xii) an erythropoietin comprising at least an opening of at least one of the cystine linkages in the erythropoietin molecule; and xiii) a truncated erythropoietin.